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Review Article—*Special issue: Thrombosis*

Acute myocardial infarction and acute stroke: What are the differences? Focus on reperfusion therapy

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ABSTRACT

This review compares acute myocardial infarction and acute stroke— their similarities and differences. The focus is given on reperfusion therapy: pharmacologic, mechanical or combined. The key trials and metaanalyses are described.

The published data on iv. thrombolysis show, that even among a subgroup of patients treated within 90 min from stroke onset the trend to lower mortality is not significant and in all other subgroups (i.e. treated after >90 min) there is a trend towards increased mortality with thrombolytic treatment.

The data on combined therapy demonstrate, that there is no benefit from facilitated intervention (iv. thrombolysis followed by ia. thrombolysis ± catheter intervention) over iv. thrombolysis alone in acute stroke. This is very similar to the situation in acute myocardial infarction 25 years ago (intracoronary thrombolysis was not superior to intravenous thrombolysis) or more recently (facilitated PCI was not shown to be superior in several trials).

The latest generation of stent retrievers is able to recanalize >70% of occluded intracranial arteries—approximately twice more compared to thrombolysis. However, it is not yet known whether this translates to better clinical outcomes. The sufficient data on clinical outcomes after primary catheter-based thrombectomy (without thrombolysis) are still missing and trials comparing iv. thrombolysis versus primary catheter-based thrombectomy are urgently needed.

The future trials in acute stroke may follow the way paved by acute myocardial infarction trials. If such trials would demonstrate superiority of catheter-based thrombectomy, we can face in future similar revolution in acute stroke treatment as we have been facing in acute MI treatment in the past years.

Contents

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1. Introduction

Acute myocardial infarction and acute stroke are two single most frequent causes of death or severe permanent disability worldwide. 20 years ago both these acute disorders caused extremely high mortality—between 20% and 30% among unselected hospital admissions. While cardiologists succeeded to decrease the in-hospital mortality of unselected acute myocardial infarction to current cca 5–8% during the last 20 years, mortality of acute stroke remained largely unchanged. The dramatic fall of mortality due to acute myocardial infarction was enabled by the introduction of reperfusion therapy: initially thrombolysis and later primary percutaneous coronary intervention (p-PCI). Specifically, the introduction of STEMI networks (effective regional cooperation between emergency medical services, local community hospitals and a tertiary cardiac center) contributed to one of the major breakthroughs in medicine changing a deadly disease into a treatable one. Many cardiologists worldwide (after having fully developed STEMI networks in their regions) are increasingly interested in acute stroke treatment. The interventional treatment of acute stroke requires effective cooperation between several medical specialties. This short review was prepared jointly by one cardiologist, one radiologist and three neurologists and deals with similarities and differences between the two diseases.

2. Similarities and differences between acute stroke and acute myocardial infarction

Table 1 shows the key similarities between these two illnesses and Table 2 the main differences. The pathophysiology of acute myocardial infarction and acute ischemic stroke is in principle similar: acute thrombotic occlusion of an artery causes ischemic necrosis of the tissue perfused by that artery. However, there is a critically important difference in the speed of necrosis development and permanent function loss. While left ventricular (LV) function can be fully restored even after 2–4 h of extensive ischemia and partial LV function recovery takes place even after 12 h of myocardial ischemia, the full recovery of all cerebral functions after moderate—large stroke is rather rare.

The etiology of acute myocardial infarction is rather uniform. Our previously published data showed, that cca 2% of patients admitted for suspected ST segment elevation acute myocardial infarction (STEMI) may have other condition mimicking an infarction [1] and that cca 7% of STEMI patients (mostly heavy smokers) do not have visible atherosclerosis but rather “pure” thrombosis in an angiographically normal coronary artery [2]. Thus over 90% of STEMI patients have the same cause of their infarction: atherosclerotic plaque rupture with superimposed in-situ arterial thrombosis. On the other hand, the etiology of acute ischemic stroke is variable: thromboembolus from the heart (e.g. in atrial fibrillation), paradoxical embolus from the venous system (via atrial septal defect or foramen ovale patens), “arteriogenic” embolus (from aorta or carotid artery), plaque rupture with in-situ thrombosis (similar to myocardial infarction), lacunar (most likely caused by a small artery occlusion, not detectable by current angiographic techniques), cryptogenic (no cause revealed), etc.

3. Reperfusion therapy

In the United States during 2009, only 4.5% of ischemic strokes were treated by iv. thrombolysis [3]. Why only a very small proportion of acute stroke patients receives reperfusion therapy when such therapy is used nearly for all patients with acute myocardial infarction? The reasons are listed in Table 3 and Fig. 1.

There are approximately 40,000 hospital admissions for stroke or TIA per year in the Czech Republic (10.5 million

Table 1 – Similarities between acute myocardial infarction and acute ischemic stroke.

	Acute myocardial infarction	*Acute ischemic stroke*
Pathophysiology	Arterial occlusion+ischemic necrosis	Arterial occlusion+ischemic necrosis
Clinical picture	Acute onset	Acute onset
Prognosis	High mortality (if untreated)	High mortality (if untreated)
Effective treatment	Reperfusion therapy	Reperfusion therapy
Thrombolytic treatment	Early reperfusion achieved in <50% of treated patients Bleeding complications may be fatal Early reocclusion is frequent	Early reperfusion achieved in <50% of treated patients Bleeding complications may be fatal Early reocclusion is frequent
Pharmaco-invasive treatment (thrombolysis+mechanical intervention)	Does not offer superior results to either method if performed alone	Does not offer superior results to either method if performed alone
Catheter-based thrombectomy	Clearly established as the most effective therapy.	Emerging as the most effective therapy

Table 2 – Differences between acute myocardial infarction and acute ischemic stroke.

	Acute myocardial infarction	*Acute ischemic stroke*
Etiology	Uniform: plaque rupture+thrombosis in situ in 90–95% patients, other causes are rare.	Multiple: cardioembolic, arterioembolic, thrombosis in situ, lacunar, cryptogenic.
Arterial occlusive thrombus feasible for catheter-based thrombectomy	Found in 95% of acute coronary angiograms	Found only in cca 35% of acute CT-angiograms
Time window symptom onset—intervention start (to offer benefit and not harm)	24 h (48 h in some patients)	3 h (8 h in some patients)
Reperfusion damage	Only theoretical, clinically always reperfusion benefit	Reperfusion damage (bleeding) is a real clinical problem
Clinical picture	Pain (dyspnoe) alerts the patient to call early for help	Neurologic dysfunction plus absence of pain causes late medical contacts in most pts.
Diagnostic method before reperfusion therapy indication	ECG (fast, simple, cheap, can be done at the site of first medical contact)	CT (takes more time, expensive, in-hospital)
Laboratory diagnostic marker	Troponin	None yet available
Contraindications for catheter-based thrombectomy	None	Intracranial bleeding or advanced ischemia on CT
Proportion of hospitalized patients who undergo reperfusion therapy	>90%	<10%

Table 3 – Possible explanations for low use of reperfusion therapy in acute stroke.

Disease related explanations	*Health care related explanations*
Many acute strokes are not suitable for reperfusion (e.g. hemorrhagic strokes)	Risks of reperfusion therapy are currently unacceptably high in pts with small strokes or TIAs
Fast development of necrosis	Many health professionals do not consider acute stroke as "superemergency" (are not aware of benefits of very early reperfusion therapy)
Risk of intracerebral bleeding (hemorhagic conversion of ischemic stroke)	
Absence of alerting symptoms (e.g. pain)	

population)—but only 120 of them are treated by catheter-based thrombectomy (CBT) and 1600 of them by thrombolysis. Two most active Czech centers perform cca 30 catheter-based thrombectomy (CBT) interventions for acute stroke annually, remaining centers between 5 and 15/year. There are approximately 30,000 hospital admissions for acute coronary syndromes (20,000 of them for acute myocardial infarction) and majority of them undergo coronary angiography with subsequent PCI or bypass surgery. Twenty-two Czech cardiology centers perform cca 15,000 PCIs for acute coronary syndromes per year. This discrepancy is striking.

4. Intravenous thrombolysis

The third International Stroke Trial (IST-3) randomized 3035 elderly (53% were >80 years) patients with acute ischemic stroke <6 h from symptom onset in two groups: (A) 0.9 mg/kg of intravenous rt-PA to a maximum of 90 mg (10% bolus with the remainder over 1 h) or (B) control treatment. Unfavorable outcome (death or disability by Oxford Handicap Score >2) at 6 months was found in 63% (rt-PA) vs. 65% (control, $p=0.181$). Fatal or non-fatal symptomatic intracranial hemorrhage within 7 days occurred in 104 (7%) patients in the rt-PA group versus 16 (1%) in the control group. Early mortality was 11% (rt-PA) vs. 7% (control group, $p=0.001$), total 6 months mortality was equal in both groups (27%). This clearly negative study is surprisingly interpreted as "despite the early hazards, thrombolysis within 6 h improved functional outcome, benefit did not seem to be diminished in elderly patients", what is difficult to understand in such a high quality journal as Lancet certainly is.

One comprehensive metaanalysis comparing iv. thrombolysis versus conservative therapy for acute stroke [4] included 26 trials involving 7152 patients. The trials tested urokinase, streptokinase, recombinant tissue plasminogen activator, recombinant pro-urokinase or desmoteplase. Most data come from trials that started treatment up to 6 h after stroke. About 55% of the data come from trials testing intravenous tissue plasminogen activator. Thrombolytic therapy increased the risk of symptomatic intracranial hemorrhage (OR 3.49, 95% CI 2.81–4.33) and death (OR 1.31, 95% CI 1.14–1.50). Thrombolytic therapy significantly reduced the proportion of patients who were dead or dependent (modified Rankin 3 to 6) at 3–6 months after stroke (odds ratio 0.81, 95% confidence interval 0.73–0.90). Treatment within <3 h of stroke appeared more effective in reducing death or dependency (OR 0.71, 95% CI 0.52–0.96) with no statistically significant adverse effect on death (OR 1.13, 95% CI 0.86–1.48). Antithrombotic drugs given soon after thrombolysis may increase the risk of death. Thus, when these data are critically interpreted, intravenous

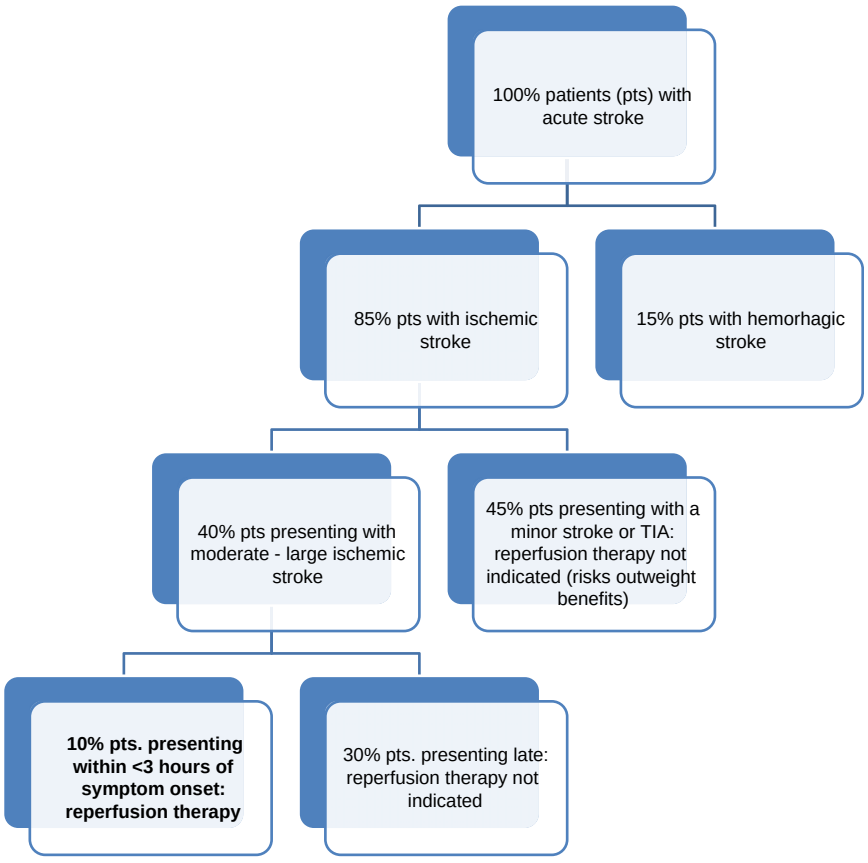

Fig. 1 – Diagram showing why only a small minority of acute stroke patients undergo reperfusion therapy.

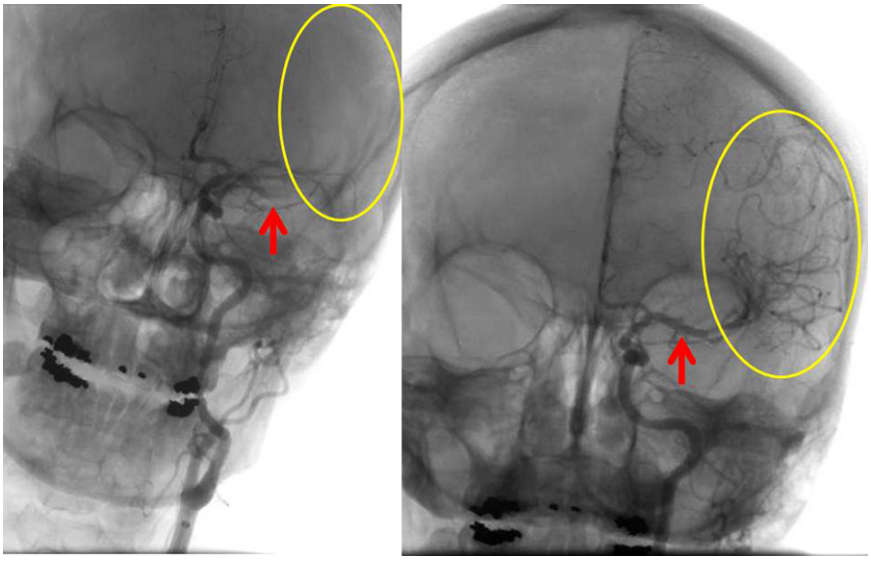

Fig. 2 – Angiography showing acute thrombotic occlusion of the medial cerebral artery (left, red arrow) with avascular ischemic territory (left, yellow circle) before catheter-based thrombectomy and (right) after the successful procedure performed with the Solitaire® stent retriever. Normalization of the previously occluded vessel segment (red arrow, right) as well as the distal perfusion (yellow circle, right) is clearly visible. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

thrombolytic therapy of acute stroke has the potential to reduce disability at the price of increasing mortality.

Even one of the two most positive thrombolytic trials [5] did not show mortality benefit (17.3% three-months mortality after thrombolysis versus 20.5% mortality after placebo, $p=0.30$). This trial found a significant decrease in overall unfavorable outcome (death or severe disability defined as mRS >2 was found in 57% after thrombolysis versus 73%

after placebo)—the difference caused by 13% absolute reduction in permanent disability. Symptomatic intracranial (6.4% thrombolysis vs. 0.6% placebo) as well as overall fatal (2.9% thrombolysis vs. 0.3% placebo) bleeding was higher after rt-PA.

The ECASS III trial [6] enrolled 821 patients treated between 3 and 4.5 h after the onset of a stroke. Less patients had an unfavorable outcome with alteplase than with placebo (48% vs. 55%; $p=0.04$). The incidence of symptomatic intracranial hemorrhage was higher with alteplase than with placebo (2.4% vs. 0.2%; $p=0.008$). Mortality did not differ significantly between the alteplase and placebo groups (7.7% and 8.4%, respectively; $p=0.68$).

Another metaanalysis [7] included 3670 patients from 8 trials using rt-PA (ECASS III, EPITHET and 6 older trials) and was focused on the time window between symptom onset and start of thrombolysis. Favorable 3-month outcome was defined as modified Rankin score 0–1. Mortality and clinically relevant parenchymal hemorrhage was analyzed. All patients were randomly allocated to alteplase or placebo. Favorable 3-month outcome increased as time delay decreased ($p=0.0269$) and no benefit of alteplase treatment was seen after around 270 min. Adjusted odds of a favorable 3-month outcome were 2.55 (95% CI 1.44–4.52) for 0–90 min, 1.64 (1.12–2.40) for 91–180 min, 1.34 (1.06–1.68) for 181–270 min, and 1.22 (0.92–1.61) for 271–360 min in favor of the alteplase group. Large parenchymal hemorrhage was seen in 5.2% of patients assigned to alteplase and 1.0% of controls, with no clear relation to time delays. Adjusted odds of mortality increased with time delay ($p=0.0444$) and were 0.78 (0.41–1.48) for 0–90 min, 1.13 (0.70–1.82) for 91–180 min, 1.22 (0.87–1.71) for 181–270 min, and 1.49 (1.00–2.21) for 271–360 min. It is surprising, that even among a subgroup of patients treated by iv. thrombolysis within 90 min from stroke onset the trend to lower mortality is not significant and in all other subgroups (treated after >90 min) there is a trend toward increased mortality with thrombolytic treatment.

5. Intra-arterial thrombolysis

Metaanalysis of 15 studies [8] on combined intravenous+intra-arterial thrombolytic therapy found 35.1% complete recanalization rate, 17.9% mortality, 51.1% unfavorable outcome (death or disability mRS >2 at 90 days) and 8.6% symptomatic intracranial hemorrhage (proven hemorrhage with an increase of NIHSS by ≥ 4 points). Neither mortality difference nor difference in symptomatic intracranial hemorrhage was found when combined lytic therapy was compared to intravenous thrombolysis alone. Eight studies included planned combination of iv.+ia. lysis, while 7 studies included only rescue ia. lysis. Only 5 studies used also mechanical (catheter-based) revascularization techniques. Medial cerebral artery was the site of thrombus in 63% of cases. Patient numbers per individual studies varied between 11 and 69, the total number of patients in the metaanalysis was 559. The mean age was 66 years, the mean baseline NIHSS was 17. The mean time delays were 135 min (symptoms—iv. lysis start) and 88 min. (iv. lysis start—angiography).

The Interventional Management of Stroke (IMS 3) trial [9] compared intravenous thrombolysis (tPA) alone vs. facilitated intervention (iv. tPA+intra-arterial tPA or mechanical thrombectomy). The trial has suspended enrollment for futility (even if the study continued, it would not show the hypothesized result that facilitated intervention is superior to iv. tPA alone). The IMS 3 was a phase 3, randomized, open-label trial that was planned to enroll subjects with a National Institutes of Health Stroke Scale (NIHSS) score of ≥ 8 treated within 3 h—656 of the planned 900 patients have been enrolled. The study was not put on hold because of safety concerns. The main results have not yet been published.

These data on combined therapy demonstrate, that there is no benefit from facilitated intervention (iv. thrombolysis followed by ia. thrombolysis $\pm$ catheter intervention) over iv. thrombolysis alone in acute stroke. This is very similar to the situation in acute myocardial infarction 25 years ago (intracoronary thrombolysis was not superior to intravenous thrombolysis) or more recently (facilitated PCI was not shown to be superior in several trials).

6. Catheter-based thrombectomy (CBT)

A few years ago CBT was performed with bulky devices and a significant risk of complications was present. In the last 3–5 years several new clot retrieval devices (stent retrievers) have been introduced and received CE mark for the use in European patients. These devices (e.g. Solitaire® or Penumbra®) are something between a tiny self expanding stent and a soft "spider-web-like" basket for clot removal and the risks of complications with this latest generation stent retrievers are much smaller, while their success rates are higher. Detailed information about CBT was published in the JACC white paper [10].

The Penumbra Pivotal Stroke Trial [11] included 125 patients mostly pre-treated by thrombolysis, with mean NIHSS 17.6 and demonstrated 81.6% recanalization rate. However, clinical outcomes were not different (or were even worse) from previous thrombolytic trials: 32.8% 90-day mortality, 75% unfavorable outcome (death or disability) and 11.2% symptomatic intracranial hemorrhage.

A recently published single center experience [12] with 104 patients treated with the Solitaire® stent retrieval, 75% of them received also thrombolysis. The recanalization rate was 78%. The mean NIHSS decreased from 15.3 (before) to 7.8 (after treatment). Mortality was 16% (anterior circulation) and 47.8% (posterior circulation). Intracranial bleeding occurred in 8%.

Another recent multicenter retrospective review [13] included 237 patients (mean age 64 years; mean baseline NIHSS 15) with acute proximal intracranial anterior circulation occlusion, endovascular treatment initiated >8 h (mean 15 h) from time last seen well. The treatment selection was strictly based on MRI or CT perfusion imaging. Successful revascularization was achieved in 74%. Parenchymal hematoma occurred in 9%. The 90-day mortality rate was 21.5% and unfavorable outcome was in 55%.

The most recent metaanalysis [14] of CBT registries identified 16 eligible published studies: 4 on the Merci device ($n=357$), 8 on the Penumbra system ($n=455$), and 4 on stent-retrievers Solitaire® or Trevo® ($n=113$). The mean procedural duration for Merci was 120 min. The mean puncture to

recanalization time for Penumbra was 64.6 min and for stent-retrievers 54.7 min. Successful recanalization was achieved in 59.1% (Merci), 86.6% (Penumbra) and 92.9% (stent-retrievers). Functional independence (mRS $\leq$2) was achieved in 31.5% (Merci), 36.6% (Penumbra) and 46.9% (stent-retrievers). The 3-month mortality rate was 37.8% in the MD studies, 20.7% in the PS studies, and 12.3% in RS studies. This study demonstrated improved outcomes after CBT when performed with the latest generation of stent-retrievers.

A recent study [15] demonstrated, that even stroke caused by the acute occlusion of the internal carotid artery (with only 17% recanalization rate and 55% mortality rate when treated by thrombolysis) can be effectively treated by CBT: successful revascularization of extracranial internal carotid artery with acute stent implantation was achieved in 95% of patients. The intracranial recanalization was achieved in 61% of patients, who had simultaneous intracranial artery occlusion. The mortality rate was 13.6% at 90 days and the unfavorable outcome (mRS>2) 59%.

These data show, that latest generation of stent retrievers (Fig. 2) is able to recanalize >70% of occluded intracranial arteries—approximately twice more compared to thrombolysis. However, it is not yet known whether this translates to better clinical outcomes. The sufficient data on outcomes after primary CBT (without thrombolysis) are still missing and trials comparing iv. thrombolysis versus primary CBT are urgently needed.

7. Future: how to improve acute stroke outcomes?

Facing the above mentioned questionable benefits from intravenous thrombolysis (versus conservative treatment) in acute stroke and absence of any benefits from intra-arterial thrombolysis (versus intravenous lysis alone) the future trials in acute stroke must follow the way paved by acute myocardial infarction trials: the future trials should compare intravenous thrombolysis alone versus catheter-based mechanical intervention alone (without lytics) for occlusion of major cerebral arteries. If such trials would demonstrate superiority of catheter-based thrombectomy, we can face in future similar revolution in acute stroke treatment as we have been facing in acute MI treatment in the past years. Nevertheless, irrespective of the trials results, the most important is to prevent acute strokes—and this field is much more successful already today. When the acute stroke occurs despite the preventive measures, the critical value of every minute shortening the delay to reperfusion therapy is essential. The continuous education should be focused on both—the wide population knowledge of stroke symptoms and the critical role of time and also to health care professionals, who must change their passive attitude to stroke treatment.

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